SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,247	02/14/2002	Lawrence M. Nogee	001107.00229	5075

22907 7590 03/10/2004

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	10/074,247	NOGEE ET AL.	
	Examiner	Art Unit	
	Juliet Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,14-17,20 and 59-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,14-17,20 and 59-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 23, 2003. Currently, claims 9-10, 14-17, 20, 59-82 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims or applicant's arguments.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Maintained Rejections

Claim Rejetions - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 9, 10, 14, 15, 16, 17, 20 and newly added Claims 59-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The invention concerns single stranded polynucleotides comprising portions of a mutant allele of a human surfactant protein C gene, wherein the polynucleotides "comprise a SNP associated with interstitial lung disease." Additional claims are directed at reagents for detecting such SNPs. The invention, as claimed, is directed towards products which, as recited in the claims encompass portions of nucleic acids associated with interstitial lung disease or detect such portions of nucleic acids. Critical to using the claimed products is the establishment of an association between particular single nucleotide polymorphisms and "interstitial lung disease."

Breadth of the Claims

With regard to the physical structure of the products themselves, claim 9 encompasses a single-stranded polynucleotide comprising 13 contiguous nucleotides of a "mutant allele" of a human surfactant protein C gene, wherein the 13 contiguous nucleotides comprise a SNP associated with interstitial lung disease. The claims have been amended to delete the recitation "of a mutant allele of a human surfactant protein C gene." The claim merely requires that the at least 13 contiguous nucleotides comprise a SNP. There is no requirement which allele of the SNP is present in the at

least 13 contiguous nucleotides. Therefore, the claim may read on the wild-type human surfactant protein C which would be suitable for use as a probe to detect the SNP. Many assays are known in the art which may distinguish between completely complementary nucleic acids and sequences which have a mismatch. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

Claim 10, recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

Claims 14-16 further define the claimed polynucleotide as comprising a label, having the SNP at the 3' or 5' end, and being on a solid support.

Claim 17 is drawn to a kit comprising a single-stranded polynucleotide comprising at least 13 contiguous nucleotides of a human surfactant protein C gene. In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include

chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). Further, Claims 59-62 have been added which also requires a single stranded polynucleotide comprising at least 13 contiguous nucleotides and instructions which are slightly different in scope.

Direction in the Specification and Working Examples

The specification teaches thirty two single nucleotide polymorphisms within the human surfactant protein C gene (referred to as the SP-C gene) (Table 1, pages 8-9) and indicates that seventeen of these were found only in patients with "lung disease." The specification does not specify how many patients were screened to obtain this set of polymorphisms, nor does the specification indicate what types of lung diseases were included in the patient sample, which lung diseases the individual SNPS were found in, or in how many patients. For those polymorphisms that were not indicated as being found only in lung diseased patients, the specification does not set forth where they were found (i.e. in what ratio in which types of patients).

The specification asserts that the disclosed SNPS can be used to identify individuals who have a predisposition for developing one of a wide variety of "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases

of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

The specification further suggests that "Association of a SNP with interstitial lung disease can be determined, for example, by statistical correlation of a disease phenotype with a particular SNP (p. 9-10)," and suggests some "well known" art methods for making such a determination.

The specification at pages 11-17 provide generic guidance as to obtaining nucleic acid samples and testing for the presence or absence of polymorphisms in nucleic acids.

Example 1 of the specification (p. 18-19) teaches a case patient full-term Caucasian female whose mother was diagnosed as having desquamative interstitial pneumonitis (DIP). The case patient developed respiratory symptoms in room air at 6 weeks of age, and an open lung biopsy showed histological features that most closely resembled cellular or non-specific interstitial pneumonitis. Control lung tissues included donor lung tissue as well as tissue from patients having end-stage pulmonary disease, including bronchopulmonary dysplasia and primary pulmonary hypertension 12

Example 2 of the specification (p. 19-20) teaches the analysis of genomic DNA by direct sequencing of PCR products and restriction analysis. The example teaches that a G to A transition was identified at the first base of intron 4 of the case patient's SP-C gene, and that no other deviations were observed in the case patient's SP-C coding sequences or intron-exon boundaries. The presence of the mutation was

confirmed in the case patient's mother, but was not found in 100 chromosomes from control subjects (p. 20).

Example 3 of the specification teaches that mature SP-C was undetectable in the lung tissue and bronchoalveolare lavage fluid of a case patient but was detected from age matched control patients (p. 21).

The specification does not provide any guidance as to which particular interstitial lung diseases (of the many various possibilities) might be associated with any of the many polymorphisms disclosed herein. The single polymorphism for which the specification provides any particular guidance, it is unclear from the teachings of the specification if the presence of the mutation is in fact indicative of any particular disease, since it was only identified in two related patients, albeit diseased patients. The specification lacks specific guidance that would enable one to conclude that in fact any of the disclosed polymorphisms are "associated with intersitital lung disease" in general (as recited in the claims) or even to conclude that any particular polymorphism disclosed herein is associated with any particular lung disease in general.

State of the Art and Level of Unpredictability

The prior art does not provide any polymorphisms in the human SP-C gene that are associated with interstitial lung disease. However, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be

associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Indeed, even the post-filing date art reiterates the unpredictability of determining an association between a SNP and a disease state. Hirschhorn *et al.* (Genetics In Medicine, 2002, Vol. 4, No. 2, p. 45-61) performed a review of association studies

between single nucleotide polymorphisms and diseases, an found that most reported associations s are not robust, of 166 putative associations which have been studied three or more times only 6 have been consistently replicated, noting that these six are probably the upper limit for the number of consistently reproducible studies due to publication bias (p. 51, Col. 1). Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2).

In the instant case, the low level of reproducibility of association studies and the unpredictability with regard to determining the relationship between SNPs is especially significant as without such a demonstrated association, one cannot determine that a particular probe or reagent would detect a SNP that is "associated with interstitial lung disease" in general or any interstitial lung disease in particular. The instant specification does not provide a robust association study for the elected SNP (claims 10 and 20), in particular, or for any of the other thirty two SNPs recited in Table 1. Even the study completed with the G to A transition was identified at the first base of intron 4 of the case patient's SP-C gene fails to establish a predictive or associative relationship between the SNP and any particular interstitial lung disease because the SNP was identified in only a single family, and therefore, it cannot be determined from the

specification the robustness of the putative association, in light of the high degree of unpredictability in this art.

Furthermore, beyond the high degree of unpredictability of the association of any of the 32 specifically disclosed SNPs and any particular interstitial lung disease or interstitial lung disease in general, it is also noted that most of the elected claims encompass reagents for the detection of any mutant allele of a human surfactant protein C gene that may be associated with interstitial lung disease, encompassing polynucleotides that comprise portions of the human surfactant protein C gene or reagents for detection of SNPS that are unknown from the specification. The structure and location of these SNPs, as well as their functionality (what disease they are associated with, for example) are not unpredictable, even given that the sequence of the genomic and coding portions of the gene were known. It is not possible to predict where a particular polymorphism would occur, or even if a polymorphism did occur, whether or not it would be associated with interstitial lung disease.

Quantity of Experimentation

In order to use the claimed polynucleotides and reagents, one would be required to undertake an extensive amount of experimentation to determine that a predictive association exists between any of the disclosed polymorphisms and any possible interstitial lung disease, or all interstitial lung diseases, as set forth in the claims. In view of the unpredictability of establishing a relationship between any single disease and a polymorphism, such study would require the screening of large numbers of patients. Furthermore, since the claims recite a generic association between

polymorphisms in the human surfactant protein C gene and any interstitial lung disease, one would be required to screen for additional polymorphisms within the gene and establish a relationship between these polymorphisms as well as those disclosed herein and any of the various interstitial lung diseases. Such experimentation would be an enormous undertaking required prior to being able to use any reagents for detecting the thirty two polymorphisms disclosed herein for detecting polymorphisms "associated with interstitial lung disease (as recited in the claims)," or to make and use reagents for detecting polymorphisms yet undisclosed.

Conclusion

Thus, having considered carefully each of these factors, that is, the lack of a guidance or working examples in the specification demonstrating that any polymorphisms in human surfactant protein C genes are "associated with interstitial lung disease," particularly the elected SNP at position 243 of SEQ ID NO: 1, the high level of unpredictability in the related art, the high degree of experimentation necessary to establish a relationship between any of the disclosed SNPs and intersititial lung disease, and the breadth of the invention, it is concluded that undue experimentation would be required to use the claimed invention, and indeed to make the claimed invention insofar as it is unclear which of the SNPs disclosed herein and not yet disclosed are in fact "associated with interstitial lung disease."

Response to Arguments

The response traverses the rejection. The response asserts that the specification enables those skilled in the art to identify additional SNPs falling within the

scope of Claim 9, for example. This argument has been thoroughly reviewed, but is not found persuasive because while the skilled artisan could conduct additional experimentation to determine whether, e.g., new SNPs within the human surfactant protein C gene might be associated with e.g., certain types of interstitial lung diseases, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue. As provided in the instant specification, seventeen of these thirty two were found only in patients with "lung disease." Upon finding a new mutation, it is unpredictable whether the SNP is associated with interstitial lung disease, since it is clear from the specification that not every SNP in the human surfactant protein C is associated with interstitial lung disease, as evidenced by the instant specification. Furthermore, as noted in the rejection above, intersitial lung disease is a very broad class of lung diseases. "Interstitial lung diseases" include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). The specification fails to provide guidance as to which SNPs are associated with which intersitial lung diseases. With respect to position 243 of SEQ ID NO: 1, the specification asserts that the SNP was found only in patients with lung disease. There is no evidence that this assertion is commensurate in scope with interstitial lung disease. For example lung disease is a much broader range of lung diseases which would also encompass lung cancer, asthma etc which do not appear to be associated in the instant application. Further, even if the specification was intended to mean interstitial lung

disease, it is unclear and unpredictable whether the mutation is found in all interstitial lung diseases or whether the mutation is only found in a subset of interstital lung diseases. There is no evidence in either the specification or the art that the genetic basis for all interstitial lung diseases is shared over the entire genus. Thus, it is unpredictable that if a SNP is associated with one particular lung disease that the SNP is similarly associated with all possible interstitial lung diseases.

It is noted that the response relies upon several post-filing date references to try to establish the enablement of the instant claims at the time the invention was made. Therefore these references do not support applicant's arguments that the specification was sufficient to enable the claimed invention at the time of filing since MPEP 2124 states. . it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 1 12, first paragraph. In re Koller, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 11.5 (CCPA 198). References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. Ex parte Erlich, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992)." However, a review of each of the references does not appear to support the position asserted by the applicant. First, Amin asserts that "the apparent absence of SP-C ...are associated with familial intersitital lung disease." The instant claims are drawn to SNPs and not to the deletion or absence of SP-C. There is no assertion in the specification that the claims are limited to SNPs which are related to the absence of SP-C. Moreover, the post filing date art of Amin provides that

"deficiency of SP-C could be due to mutations of the Sp-C gene, decreased transcription, translation, processing and secretion by alveolar type II pneumocytes or change sin catabolism of the protein. The absence of identifiable mutations in the SP-C gene suggest that the defect in these patients is mediated at the transcriptional or post-transcriptional level. However a mutation in the promoter region, introns, or 3' UTR region that affects SP-C expression could have been missed" (page 90-91 of Amin). It is clear from the post filing date art that the art has not identified a particular mechanism which the skilled artisan could use to identify SNPs in the gene as indicative of intersititial lung disease. Thus, the statement that the absence of SP-C is associated with intersititial lung disease is not commensurate in scope with the instant claims since the claims are not limited to SNPs which cause an absence of SP-C.

The response provides Thomas, another post-filing date article, identifies a new mutation which is associated with interstitial pneumonitis (a particular interstitial lung disease). This does not support the assertion that each SNP in SP-C is associated with each intersitial lung disease. The assertion that the presence of a single mutation in two different pathological diagnoses in affected relatives sharing this mutation ndicates that this kindred, these disease may represent pleiotropic manifestations of the same central pathogenesis. First, the art is post filing date and there is nothing to suggest at the time the invention was made, the skilled artisan would have predicted that a single SNP is associated with a variety of interstitial lung diseases. Second, the art of Thomas is directed to a SNP not present in the instant application. Finally, the art does not provide a certain relationship between all interstitial lung diseases, but provides that

there MAY be a central pathogenesis. It would require further undue experimentation before the skilled artisan would be able to use the information for association with all interstitial lung disease. Similarly, the response also provides Nogee, Pantelidis and Hamvas, as post-filing date art. None of these references support the assertion that each SNP in SP-C is associated with each intersitial lung disease. Pantelidis suggest that "the recent finding of surfactant gene variations in familial and nonfamilial ILD opens up a new area for more detailed analysis to explore whether these variations play a role in a wider range of ILDs" (4/7 of Pantelidis). This passage clearly suggests that at the time the article was written the skilled artisan clearly did not recognize that each SNP or mutation is associated with all ILDs. Thus, at the time the instant application was filed, the skilled artisan would be required to perform additional undue experimentation to determine whether gene variations play a role in a wider rang of ILDs. The mutation discussed in Hamvas is not within the scope of the claims, i.e. it is a deletion, not a SNP, thus the arguments are moot. However, Hamvas does state that "the consequences of mutations on pulmonary surfactant composition and function are poorly understood" (abstract) such that Hamvas required additional experimentation to analyzed the effect of the mutations.

As explained above, post-filing date publications can not be used to support enablement of the invention (see MPEP 2124).

The response asserts that there is no reason to think that the association between disclosed SNPs and interstitial lung disease occurs only in specific populations (page 16 of response filed December 23, 2003). This argument has been thoroughly

reviewed, but is not found persuasive because as provided by MPEP 716.01(c) "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the association of SNPs and disease is arguments alone. The action provides evidence that mutations vary in populations which is not rebutted by any particular evidence, merely attorney arguments.

The response states that Pennisi is not relevant because the claims are not directed to identifying key genes as associated with a disease. This argument has been thoroughly reviewed, but is not found persuasive because the art and the specification illustrate that associating the SP-C gene with interstitial lung disease is not predictable. As provide din the instant specification approximately ½ of the mutations do not appear to be associated with disease state. Further, there is no evidence that all interstitial lung diseases act concordantly. In fact the references provided by applicant appear to indicate that the post filing date art does not treat all interstitial lung diseases as a group (see Pantelidis, for example).

The response argues that Blumenfeld is not relevant to Claims 10, 20, 60 and 62, however the response does not provide any argument with respect to the generic

claims. Further, Hirschhorn was provided as evidence that association between mutations and disease is not always predictable.

While one could conduct additional experimentation to determine whether, e.g. particular SNPs or newly discovered SNPs might be associated with e.g. any one of the numerous number of interstitial lung disease, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. It is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention as broadly as claimed. It would require undue experimentation for a skilled artisan to use the claimed invention.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Written Description

5. Claims 9, 10, 14, 15, 16, 17, 20 and newly added Claims 59-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to the physical structure of the products themselves, claim 9 encompasses a single-stranded polynucleotide comprising 13 contiguous nucleotides of a human surfactant protein C gene, wherein the 13 contiguous nucleotides comprise a

SNP associated with interstitial lung disease. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

Claim 10, recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

Claims 14-16 further define the claimed polynucleotide as comprising a label, having the SNP at the 3' or 5' end, and being on a solid support.

Claim 17 is drawn to a kit comprising a single-stranded polynucleotide comprising at least 13 contiguous nucleotides of a human surfactant protein C gene. In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). Further, Claims 59-62

have been added which also requires a single stranded polynucleotide comprising at least 13 contiguous nucleotides and instructions which are slightly different in scope.

The specification recites thirty two single nucleotide polymorphisms within the human surfactant protein C gene, but as discussed in the enablement rejection, the specification does not demonstrate which of these are "associated with interstitial lung disease," as required by the claims. Instant SEQ ID NO: 1 and nucleic acids consisting of fragments of SEQ ID NO: 1 that contain the polymorphic sites are described.

The claims, being drawn to "comprising" language encompass polynucleotides that have as few as 13 nucleotides in common with the human surfactant C protein, but are contained within any context, as exemplified by the prior art applied under 102. The structural language in the claims encompasses a vast array of possible polynucleotides that are not described in the specification. Applicant has not demonstrated possession of any possible polynucleotide that **comprises** 13 contiguous nucleotides of any version of a human surfactant protein C gene that contains a SNP associated with intersitital lung disease, since there are hundreds of thousands of possible nucleic acids that comprise such nucleic acids. This rejection applies to claims 10 and 20 insofar as they are also drawn using "comprising" language. Amendment of these claims to clarify that the claimed polynucleotide "consists of" a fragment of instant SEQ ID NO: 1 that includes position 243 (elected SNP) of instant SEQ ID NO: 1 would overcome this rejection with regard to claims 10 and 20.

In addition, the generic claims include polynucleotides that comprise the human surfactant C gene that is associated with interstitial lung disease. The specification has

described thirty two possible polymorphisms, but these are not joined by any structural characteristic such that one could readily predict other possible polymorphisms within this gene, either in the coding region as given in SEQ ID NO: 1, or in the genomic sequence which is not recited in the specification. The "functional language" that defines these SNPs as being associated with interstitial lung disease does not lead one to a predictable structure that would allow one to determine even which of the 32 polymorphisms disclosed in the specification meet the requirement of being "associated with interstitial lung disease," let alone any SNP that has not been described explicitly in the specification.

Because of these deficiencies, the claims are rejected as lacking adequate written description.

Response to Arguments

The response traverses the rejection. The response asserts that a representative number of molecules has been provided such that written description has been satisfied. This argument has been reviewed but is not convincing because as explained above, the claims minimally read on any nucleic acid which comprises at least 13 nucleotides from the human SP-C gene which encompass a SNP. This broad recitation reads on any nucleic acid from a dog, a monkey or other homologous sequences which have not been described. Further the claim reads on additional mutations which have not been described by the instant specification. The instant specification has provided no guidance homologous sequence of the human SP-C gene which may be encompassed by the instant claims.

Furthermore, as pointed out by the post-filing date art, the claims read on SNP's which were not described in the instant application. As provided in Example 11 of the Written Description Guidelines, provides that the general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection/Objection Necessitated by Amendment

Claim Objections

6. Claims 59-62 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 17, 20. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

It is noted that the claims only differ in the instructions within the kit. For example the instructions of Claim 17 are for a method of screening an individual for a predisposition to developing intersistial lung disease whereas the instructions for Claim 59 are directed to a method to aid in diagnosing an individual for a predisposition to

developing intersistial lung disease and further, the instructions of Claim 61 are for a method of screening an individual for having the interstitial lung disease to determine whether the individual is likely to respond to a therapeutic intervention. Each of the instructions have the same use. Thus, the claims do not have different components. Further, instructions do not carry patentable weight. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 9, 10, 15, 63-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Hudson (Genbank Accession Number G11963, October 1995).

The claims are drawn to a single stranded polynucleotide comprising at least 13 contiguous nucleotides of SP-C which comprise a SNP and may be used as a probe. Hudson teaches a nucleic acid sequence of 356 nucleotides in length which comprise 17 contiguous nucleotides from SEQ ID NO: 1, namely positions 227-243 of SEQ ID NO: 1. The polynucleotide spans a nucleotide position of 243 of SEQ ID NO: 1 (limitations of Claim 10). These 17 contiguous nucleotides are 100% identical to

positions 334-318 of the human sequence of Hudson (limitations of Claim 9, 63-64). Hudson teaches that the genomic DNA (i.e. double stranded) is amplified using primer A and B by denaturation, therefore, the sequence of Hudson is single stranded at this point such that the instant claim is anticipated.

With respect to Claim 15, the SNP is at the 3' end. 3' end has been broadly interpreted to mean 3' of the middle of the sequence. Therefore anything 3' of position 200 of Hudson is at the 3' end of the polynucleotide. The 3' end has not been interpreted to mean the 3' terminus or the final nucleotide.

With respect to Claims 65-67 the claims are direct to the polynucleotides that comprises at least 20, 25, 50 contiguous nucleotides. Hudson teaches a nucleic acid of 356 contiguous nucleotides. The claim does not appear to require 20, 25, 50 contiguous nucleotides of SEQ ID NO: 1 or even of the human SP-C gene.

8. Claims 9, 10, 63-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. (Genbank Accession Number T64088, February 1995).

Hillier teaches a nucleic acid cDNA clone for the pulmonary surfactant-associated protein C which comprises 60 nucleotides of SEQ ID NO: 1 which spans position 49 (limitations of Claim 9, 10, 63-67). The polynucleotide of Hillier is 83 nucleotides in length wherein positions 38-97 of SEQ ID NO: 1 are 100% identical to position 18-77 of Hillier's sequence. Hillier teaches that the nucleic acid was cloned into a vector, therefore at a point in the cloning the sequence was single stranded, as required by the instant claims.

With respect to Claim 15, the SNP is at the 5' end. 5' end has been broadly interpreted to mean 5' of the middle of the sequence. Therefore anything 5' of position 40 of Hillier is at the 5' end of the polynucleotide. The 5' end has not been interpreted to mean the 5' terminus or the first nucleotide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 17, 20, 59-62, 68-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudson (Genbank Accession Number G11963, October 1995) in

view of Ahern (The Scientist, Vol. 9, #15, p. 20, July 1995, provided as HTML print out pages 1-5).

Hudson teaches a nucleic acid sequence of 356 nucleotides in length which comprise 17 contiguous nucleotides from SEQ ID NO: 1, namely positions 227-243 of SEQ ID NO: 1. The polynucleotide spans a nucleotide position of 243 of SEQ ID NO: 1 (limitations of Claim 10). These 17 contiguous nucleotides are 100% identical to positions 334-318 of the human sequence of Hudson (limitations of Claim 9, 63-64). Hudson teaches that the genomic DNA (i.e. double stranded) is amplified using primer A and B by denaturation, therefore, the sequence of Hudson is single stranded at this point such that the instant claim is anticipated. With respect to Claim 15, the SNP is at the 3' end. 3' end has been broadly interpreted to mean 3' of the middle of the sequence. Therefore anything 3' of position 200 of Hudson is at the 3' end of the polynucleotide. The 3' end has not been interpreted to mean the 3' terminus or the final nucleotide. With respect to Claims 68-82 the claims are direct to the polynucleotides that comprises at least 20, 25, 50 contiguous nucleotides. Hudson teaches a nucleic acid of 356 contiguous nucleotides. The claim does not appear to require 20, 25, 50 contiguous nucleotides of SEQ ID NO: 1 or even of the human SP-C gene.

Hudson does not teach a kit which includes instructions.

Ahern teaches biochemical reagent kits, and teaches that such kits are convenient for scientists because they put the reagents needed for a particular assay all together for a scientist to use (p. 4). Ahern further teaches that biochemical kits provide

a further advantage to customers because they provide detailed instructions to follow (p. 4).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Hudson with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the probes, and reagents of Hudson or Hillier into a kit, as taught by Ahern for the express purpose of saving time and money. It would have been prima facie obvious to one of ordinary skill in the art to have modified the kit taught by Halverson *et al.* so as to have included instructions, as taught by Ahern. One would have been motivated to make such an inclusion in order to have provided an additional advantage to users of the kit that is to direct them as to how to use the reagents contained in the kit. Furthermore, it is noted that the actual content of the instructions "i.e. for a method of detecting the SNP" is considered to be a statement of intended use for the claimed kits. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The content of the instructions of the instant kit are not considered to distinguish the claimed kits over the prior art.

11. Claims 17, 20, 59-62, 68-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier et al. (Genbank Accession Number T64088, February 1995) in view of Ahern (The Scientist, Vol. 9, #15, p. 20, July 1995, provided as HTML print out pages 1-5).

Hillier teaches a nucleic acid cDNA clone for the pulmonary surfactant-associated protein C which comprises 60 nucleotides of SEQ ID NO: 1 which spans position 49 (limitations of Claim 9, 10, 63-67). The polynucleotide of Hillier is 83 nucleotides in length wherein positions 38-97 of SEQ ID NO: 1 are 100% identical to position 18-77 of Hillier's sequence. Hillier teaches that the nucleic acid was cloned into a vector, therefore at a point in the cloning the sequence was single stranded, as required by the instant claims. With respect to Claim 15, the SNP is at the 5' end. 5' end has been broadly interpreted to mean 5' of the middle of the sequence. Therefore anything 5' of position 40 of Hillier is at the 5' end of the polynucleotide. The 5' end has not been interpreted to mean the 5' terminus or the first nucleotide.

Hillier does not teach a kit which includes instructions.

Ahern teaches biochemical reagent kits, and teaches that such kits are convenient for scientists because they put the reagents needed for a particular assay all together for a scientist to use (p. 4). Ahern further teaches that biochemical kits provide a further advantage to customers because they provide detailed instructions to follow (p. 4).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Hillier with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the probes, and reagents of Hudson or Hillier into a kit, as taught by Ahern for the express purpose of saving time and money. It would have been prima facie obvious to one of ordinary skill in the art to

have modified the kit taught by Halverson *et al.* so as to have included instructions, as taught by Ahern. One would have been motivated to make such an inclusion in order to have provided an additional advantage to users of the kit, that is to direct them as to how to use the reagents contained in the kit. Furthermore, it is noted that the actual content of the instructions "i.e. for a method of detecting the SNP" is considered to be a statement of intended use for the claimed kits. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The content of the instructions of the instant kit are not considered to distinguish the claimed kits over the prior art.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C Switzer
Examiner
Art Unit 1634

March 5, 2004